Gennrich, Jane - Medicaid

From: Eide, Tamara J. - Medicaid
Sent: Thursday, April 24, 2014 4:56 PM
To: Gennrich, Jane - Medicaid
Subject: FW: P&T Written Submission
Attachments: ID - Inhaled & Enzymes - 5.14.14.pdf; Chronic Care Guidelines.AJRCCM.2013.pdf; PERT bulletin - Final_New Logo.pdf

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From: Erdo, Jackie [mailto:jerdo@cff.org]
Sent: Thursday, April 24, 2014 11:18 AM
To: Eide, Tamara J. - Medicaid
Subject: P&T Written Submission

Dear Dr. Eide,

Please find attached a written submission from the Cystic Fibrosis Foundation for Idaho's upcoming P&T review, as well as supplemental evidence-based materials. We hope the Committee will consider us a resource moving forward.

Thank you,

Jacqueline Erdo
Public Policy Specialist
Cystic Fibrosis Foundation National Office
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CYSTIC FIBROSIS
FOUNDATION
ADDING TOMORROWS

Tami Eide, Pharm.D.
Idaho Medicaid
Pharmacy & Therapeutics Committee
3232 Elder Street
Boise, Idaho 83705

Dear Colleagues,

On behalf of patients and families with cystic fibrosis (CF), we write to recommend that Idaho Medicaid provide coverage on the preferred drug list (PDL) for all FDA-approved pancreatic enzyme products and inhaled antibiotics designed for the treatment of CF. Cystic fibrosis is a genetic disease wherein manifestations and symptoms can vary widely from patient to patient. With an already limited treatment arsenal we fear that the exclusion of available treatments would place people with CF at serious risk for negative health outcomes and irreversible lung damage.

As a recognized expert in CF, the Cystic Fibrosis Foundation accredits 115 care centers and 60 affiliate programs nationally that provide treatment and care in accordance with systematically reviewed clinical practice guidelines. Treatment options for this rare, life-threatening disease are extremely limited. Both the inhaled antibiotic and pancreatic enzyme classes contain products that are vital and necessary for effective CF treatment. Without open access to all FDA-approved treatment options, it is our contention that restrictions could result in severe health consequences for patients and greater health care costs.

PANCREATIC ENZYME PRODUCTS

Selecting one enzyme as a preferred product disregards the variable clinical responses of CF patients to pancreatic enzyme therapies, ignores the lack of published comparative clinical trial data supporting substitution, and jeopardizes patient health by requiring individuals to fail on one therapy prior to using another. Nutritional failure of any type for CF patients is unacceptable as it places them at risk for long-term health consequences. 85-90 percent of cystic fibrosis patients have pancreatic insufficiency requiring them to take pancreatic enzyme replacement therapy (PERT) with every meal and snack for the duration of their lives to prevent abdominal distress and malabsorption of calories and nutrients. Nutritional status is closely linked to pulmonary function and survival and failure of pancreatic enzyme therapy can have significant short-term consequences as well as implications for patient survival.

The dissolution properties of the PERTs are not identical; individual patients can have a variable response that cannot be predicted. Because pancrelipase is destroyed in an acidic environment, all PERTs have a pH-dependent polymer coating which is intended to release the pancrelipase in the more pH-neutral environment of the intestine. The enteric coating for each of the FDA-approved products is different. The degree of acidification of the GI tract in each CF patient varies, which may be why some patients have a better clinical response to one product over another. In addition, the coating process differs among products; some are microtablets and some are microspheres, with

the size of these microcapsules also varying. The size determines when gastric emptying of pancrelipase occurs and how well it is dispersed throughout the meal. Demanding failure on one PERT before prescribing another places CF patients at risk for nutritional failure and potential hospitalization. For people with this chronic and progressive disease, step therapy poses an unjustifiable risk.

INHALED ANTIBIOTICS

Inhaled antibiotics are used to improve respiratory symptoms in people with cystic fibrosis with *Pseudomonas aeruginosa*, a bacterium that often chronically infects the lungs of people with CF and is associated with increased morbidity and mortality. Due to the rise of antibiotic resistance in this intensely treated population, treatment options are limited. Cayston®, TOBI®, and the TOBI® Podhaler® represent important additions to the CF therapeutic arsenal. We recommend access to all inhaled antibiotics for people with cystic fibrosis as treatment choice should be left to the physician.

Although TOBI® is a significant therapy for CF, it can only be used for a 28-day course. Patients must wait another 28-day cycle before taking another course of this aerosol antibiotic. During the 28-day interval without TOBI®, there was no FDA approved inhaled antibiotic to meet the patients' medical needs until the approval of Cayston®. Use of Cayston® has been shown to decrease *P. aeruginosa* in sputum, reduce the number of pulmonary exacerbations patients experience, and improve lung function and quality of life in people with CF. Despite the importance of chronic anti-pseudomonal therapy in CF, about one-third of infected individuals over 6 years old do not use TOBI® long-term, and among those who do use it, only 46% of the medicine prescribed is actually taken. Appearance of antibiotic resistance, drug toxicity, and the long amount of time required to inhale the drug (>35 min/day) likely all contribute to the low treatment uptake. However, the TOBI® Podhaler®, a new delivery mechanism for TOBI®, is designed to improve adherence and patient outcomes. We believe that the best way to ensure patient health is to provide access to all treatment options for people with cystic fibrosis and allow the provider (experts in CF treatment) to determine which therapy will be most effective for their patient.

Limiting patient choice for enzymes and inhaled antibiotics can contribute even greater health difficulties to those already experienced by people with cystic fibrosis. We strongly urge you to ensure that CF patients and providers have the ability to choose the most appropriate treatment given the patient's unique health profile and thereby attempt to minimize the risk of further medical complications.

We look forward to working with you further on this important issue and hope that you find the attached information useful.

Sincerely,

Bruce C. Marshall, M.D.
Senior Vice President of Clinical Affairs

Mary B. Dwight
Senior Vice President for Policy & CF Community Affairs

CYSTIC FIBROSIS FOUNDATION
ADDING TOMORROWS

CYSTIC FIBROSIS FOUNDATION INFO-POD
Information You Need to Make Benefits Decisions

Issue: Pancreatic Enzyme Replacement Therapy (PERT)

Summary: Cystic fibrosis (CF) causes pancreatic insufficiency (PI) in approximately ninety percent of patients, resulting in maldigestion and malabsorption of nutrients (1). The long term consequences of malnutrition are significant and include permanent stunting of stature (2, 3), cognitive dysfunction linked to vitamin E deficiency (4, 5) and more rapid decline in pulmonary function (6-11). The treatment of PI with pancreatic enzyme replacement therapy (PERT) at every meal and snack is life-sustaining and can help prevent the most severe consequences of CF. Although all pancreatic enzyme products (PEP) contain the same core digestive enzymes, different formulations work better in different patients, and access to multiple products is essential for optimal treatment. Currently, three products (Creon®, Pancreaze®, and Zenpep®) are FDA-approved for use in the United States.

What is cystic fibrosis?

Cystic fibrosis is the most common life-threatening genetic disease in the US, affecting approximately 30,000 individuals. Lung disease is the major cause of disability and death, causing 80% of deaths in CF (12).

In the last few decades, improvements in care, including aggressive treatment of lung infections (13) and increased attention to nutritional deficits (14), have resulted in people with CF living into their 30s, 40s and beyond (15). Preserving lung function and maintaining optimal nutritional status are thus vital to the health of the individual with CF.

What effect does CF have on nutritional status?

Progressive destruction of the pancreas, with scarring and clogging of pancreatic ducts, begins before birth in the great majority of individuals with CF. The resulting pancreatic insufficiency means these patients are unable to digest and absorb nutrients properly, causing a deficiency in both calories and vitamins. Chronic lung infections further drain nutritional resources; thus, the exacerbations of CF lung disease that frequently occur are associated with weight loss and growth retardation (8).

Conversely, improving nutritional status has been shown to improve pulmonary outcomes and survival (14). *Thus, optimizing nutritional status is a key component in the care of the individual with CF.*

Careful monitoring of vitamin levels, growth, and other nutritional indicators is necessary to help CF dietitians and physicians detect and treat problems before they produce permanent stunting and lung disease. Normal growth and nutrition should be the goal for every individual with CF. This is achievable only by:

- providing plenty of high-calorie foods;

- supplementing with fat-soluble vitamins; and
- supplying appropriate pancreatic enzyme products to be taken with every meal and snack.

What are Pancreatic Enzyme Products?

Pancreatic enzyme products are capsules containing small pellets of digestive enzymes (amylases, proteases, and lipases). The pellets are enteric-coated to allow them to pass through the acidic conditions in the stomach without losing activity. The coating on the enzymes dissolves in the more basic environment of the small intestine, releasing the digestive enzymes to interact with food as it moves through the gastrointestinal tract.

Why is the FDA requiring new regulation of PEPs?

Although PEPs have been available for decades, the FDA recently began requiring manufacturers to validate these products for safety and efficacy according to FDA guidelines. Formerly, enzyme activities in many PEPs varied significantly from values stated on the labels; inconsistencies were also identified in bioavailability, effectiveness, composition, and manufacturing (16). While malabsorption and intestinal blockages can result from inadequate PERT (17, 18), excessive enzyme dosing has been associated with problems such as hyperuricosuria (19) and fibrosing colonopathy, a severe intestinal fibrotic process associated with colonic strictures (20).

All PEPs sold in the US now must be made under approved laboratory conditions and meet strict requirements for safety and efficacy. Currently, three products (Creon®, Pancreaze®, and Zenpep®) are FDA-approved for use in the United States. Additional products, some of which were formerly available in other formulations, are under regulatory review.

Why do we need a variety of PEPs ?

Variations in digestive processes, both between different individuals and within the same individual as they age, means that a single PEP may not work optimally for all those with CF throughout their lives. People exhibit differences in appetite, diet, transit time of food through the gastrointestinal tract (21), and intestinal pH (22). Because enteric coatings differ in the rate and pH at which they dissolve (23-26), and types and ratios of enzymes present in various products also differ, some PEPs may work better in some environments, while others may work better under other conditions (17, 27, 28). It is, therefore, not unusual for patients to try several different products before finding one that is right for them. Formal comparator studies have not been performed with the current PEPs, thus the best guide for successful enzyme treatment is the experience of CF care centers, which has shown that a variety of PEPs are needed by their patient population.

What is the recommended dosing for PEP?

PEPs must be given with every meal and snack. In the past, labeled doses did not reflect actual enzyme activity, and so there are no true dose-response studies available. Thus, there is no known, clear relationship between increasing PEP dose per gram of fat taken and fat absorption (29) or growth (30) in patients who are

clinically stable. Dosing is based on historical and consensus recommendations: 2-5,000 lipase units per 120 ml of feeding (31) and 500-2,500 lipase units/kg/meal beyond infancy (11), with the lower end of the dosing range recommended for older patients and the higher end recommended for younger patients, who take in proportionately more fat. To help avoid serious complications such as fibrosing colonopathy, enzyme doses should not exceed 2,500 lipase units/kg/meal or 4,000 lipase units/gram fat per day (32).

Patients with CF are encouraged to eat several snacks each day to improve their caloric intake; consequently, they may be taking doses of PEPs up to 6 times a day. Snacking without PEPs can result in loss of important calories, as well as intestinal obstruction and hospitalizations (18). In addition, some patients use nocturnal tube feedings and may require additional doses before or even in the middle of their tube feedings. For this reason, patients with CF should not have limitations on the amount of PEPs that are prescribed each month.

The adequacy of enzyme therapy can be assessed subjectively by following growth parameters and stool patterns. Historically successful treatments suggest that optimal therapy requires careful monitoring and dose adjustment as caloric requirements change with age or with the effects of advancing disease.

How are PEPs administered?

Infants and young children may open the capsules and take the microencapsulated beads mixed in an acidic food such as applesauce, or directly into their mouths. The enteric coating on the beads should not be destroyed by chewing or crushing, which would result in inactivation of the enzymes as they pass through the stomach.

Antacids or H2 antagonists may be useful in some individuals to improve dissolution of the enteric coating and enzyme release (33). If enzymes are not released high in the GI tract, much of the absorptive surface will be bypassed, leading to suboptimal food absorption.

Who will benefit from receiving PEPs?

Some pancreatic sufficient patients with CF and recurrent pancreatitis may need to take enzyme supplements. All patients with CF who are pancreatic insufficient will benefit from the new PEPs. This treatment will be life-long and needs to be taken with every meal and snack.

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Occasional Essay

Cystic Fibrosis Pulmonary Guidelines

Chronic Medications for Maintenance of Lung Health

Peter J. Mogayzel, Jr.[1], Edward T. Naureckas[2], Karen A. Robinson[3], Gary Mueller[4], Denis Hadjiliadis[5], Jeffrey B. Hoag[6], Lisa Lubsch[7], Leslie Hazle[8], Kathy Sabadosa[8], Bruce Marshall[8], and the Pulmonary Clinical Practice Guidelines Committee*

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Rationale: **Cystic fibrosis (CF) is an autosomal recessive disease characterized by abnormal airways secretions, chronic endobronchial infection, and progressive airway obstruction. The use of medications to slow the progression of lung disease has led to significant improvement in survival. An evidence review of chronic medications for CF lung disease was performed in 2007 to provide guidance to clinicians in evaluating and selecting appropriate treatment for individuals with this disease. We have undertaken a new review of the literature to update the recommendations, including consideration of new medications and additional evidence on previously reviewed therapies. A multidisciplinary committee of experts in CF pulmonary care was established to review the evidence for use of chronic medications for CF lung disease and make treatment recommendations. Published evidence for chronic lung therapies was systematically reviewed and resulting treatment recommendations were graded based on the United States Preventive Services Task Force scheme. These guidelines provide up-to-date evidence of safety and efficacy of chronic treatments of CF lung disease, including the use of novel therapies that have not previously been included in CF pulmonary guidelines.**

Keywords: antibiotics; antiinflammatory agents; bronchodilators; CFTR modulators; hypertonic saline

To aid care providers in the use of chronic medications, the Cystic Fibrosis (CF) Foundation established the Pulmonary Clinical Practice Guidelines Committee, which published guidelines on chronic medications for the maintenance of lung heath in 2007 (1). Since this publication, two novel medications have been approved for use in the United States and additional data have been published on therapies previously reviewed. To consider this new evidence, as well as additional and revised questions on the use of therapies, the committee conducted an assessment of the current evidence to develop the updated recommendations presented here.

METHODS

A multidisciplinary committee composed of 17 members reviewed the 2007 guidelines and developed a series of questions related to chronic drug therapies for CF. An evidence review was commissioned from The Johns Hopkins University, with systematic reviews completed for each question. New reviews were conducted for each question, as some questions were new or revised, new medications and indications were considered, and because a full systematic review was not completed for all questions in the development of the 2007 guidelines. The review was limited to parallel and cross-over randomized controlled trials (RCTs). Members of the committee disclosed any potential conflicts of interest. If any perceived conflict was present, members did not participate in any discussions or decisions on recommendations regarding that therapy.

Subcommittees were created to review the evidence summaries and draft recommendations for presentation to the entire committee. Final recommendations were graded using the U.S. Preventive Services Task Force scheme, which encompasses an estimate of net benefit and certainty of net benefit (2) (Table 1). Detailed methods are contained in the online supplement (E1).

RESULTS

The search identified a total of 6,898 unique citations, of which 57 were included in the 2007 guidelines (Figure 1). The current guidelines are based on review of 137 articles describing 84 studies (Table 2). Because some questions addressed herein differ from those posed in the 2007 guidelines, 14 studies reviewed previously were not included in the current literature review. A summary of the recommendations can be found in Tables 3 and 4.

Unchanged Recommendations from Previous Guidelines

The current committee affirmed previous recommendations for several therapies, which can be found in Table 3. A comprehensive review of these recommendations can be found in the online supplement (#2).

Updated Recommendations of Previously Reviewed Medications

β_2-Adrenergic receptor agonists. The 2007 guidelines recommended the use of β_2-adrenergic receptor agonists based on an

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*A complete list of the Pulmonary Clinical Practice Guidelines Committee can be found before the REFERENCES.

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Author Contributions: All authors and committee members participated in review of the literature and development of recommendations and review of the manuscript. The following authors formed a writing subcommittee to compose the manuscript: P.J.M., E.T.N., K.A.R., G.M., D.H., J.B.H., L.L., L.H., K.S., and B.M. P.J.M. and E.T.N. were primarily responsible for editing the manuscript. K.A.R. was responsible for conducting the systematic review.

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

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TABLE 1. U.S. PREVENTIVE SERVICES TASK FORCE EVIDENCE GRADING

	Magnitude of Net Benefit (Benefit Minus Harms)			
Certainty of Net Benefit	Substantial	Moderate	Small	Zero/Negative
High	A	B	C	D
Moderate	B	B	C	D
Low	I (insufficient evidence)			

The overall strength of the evidence is based on the certainty of the magnitude of benefit defined as benefit minus harm. Adapted by permission from Reference 39.

Strength of Recommendation:

A. The committee strongly recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is substantial.

B. The committee recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial.

C. The committee recommends that clinicians consider providing this therapy to selected patients depending on individual circumstances. However, for most individuals without signs or symptoms there is likely to be only a small benefit from this service.

D. The committee recommends against the therapy. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits. Clinicians should discourage the use of this service.

I. The committee concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

Quality of the Evidence:

High. The available evidence includes consistent results from well designed, well conducted studies in representative populations. This conclusion is therefore unlikely to be strongly affected by the results of future studies.

Moderate. The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: the number, size, or quality of individual studies; inconsistency of findings across individual studies; limited generalizability of findings to routine primary care practice; lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.

Low. The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: limited number or size of studies; important flaws in study design or methods; inconsistency of findings across individual studies; gaps in the chain of evidence; findings not generalizable; lack of information on important health outcomes. More information may allow estimation of effects on health outcomes.

appraisal of the Cochrane Review of both short-acting and long-acting β_2-adrenergic receptor agonists. The Cochran Review was updated in 2011 (3), and includes 18 studies with 369 participants. Given that the majority of these studies were of short duration, the committee reviewed the literature on the chronic use of these medications. We found only two RCTs ranging in size from 20 to 30 participants. König and coworkers (4) investigated albuterol (180 μg by metered dose inhaler) twice daily for 6 months, and reported statistically significant increases in FEV_1 (12.1%), FVC (8.2%), and forced expiratory flow between 25% and 75% of FVC ($FEF_{25-75\%}$; 17.2%) from baseline compared with placebo. Eggleston and coworkers (5) used a cross-over design and evaluated the same dose of albuterol given four times daily over 4 months, in methacholine challenge responders versus nonresponders, as compared with placebo. However, no significant differences were seen in percent change in FEV_1, FVC, and $FEF_{25-75\%}$ compared with baseline for any of the groups. The evidence that the β_2-adrenergic receptor agonists favorably impact other important outcomes, such as exacerbations or quality of life (QOL), was relatively weak.

Short-term administration of β_2-adrenergic receptor agonists can benefit those individuals with airway hyperresponsiveness (3), which is common in individuals with CF (6). These medications also have value in preventing bronchospasm associated with inhaled therapies. However, there is insufficient evidence to recommend chronic, daily use of a β_2-adrenergic receptor agonist. The committee rated the overall certainty of net benefit as low, and, therefore, cannot recommend for or against the chronic use of β_2-adrenergic receptor agonists.

Oral, nonsteroidal antiinflammatory drugs. The 2007 guidelines recommended the use of ibuprofen to prevent the loss of lung function in individuals with FEV_1 greater than 60% predicted. In addition to the three RCTs of oral, nonsteroidal antiinflammatory drugs that included 145 total patients reviewed previously (7–9), an additional RCT comparing ibuprofen to placebo in 142 patients aged 6–18 years was identified (10). A Cochrane Review that evaluated the same studies concluded that high-dose ibuprofen can slow the progression of lung disease in people with CF, especially in children (11).

Based on our review of the literature, the committee narrowed the previous recommendation to include only children 6–17 years of age, rating the certainty and magnitude of net benefit as moderate. Because of the scant data focusing on individuals with CF 18 years of age or older, the committee felt that there was insufficient information to make a recommendation for the adult population.

Studies of ibuprofen on neutrophil migration suggest that neutrophil migration increases rather than decreases at lower serum levels (12). Thus, maintaining an ibuprofen serum concentration of 50–100 μg/ml should be considered a key aspect of ibuprofen therapy, and has, therefore, been included in the current recommendation.

Azithromycin. The 2007 guidelines recommended the use of azithromycin in individuals with persistent *Pseudomonas aeruginosa* in airway cultures. We also sought to determine the value of this therapy in individuals without *P. aeruginosa* infection. We identified five RCTs (13–17), three of which were not included in the prior guidelines (13, 14, 17), and one cross-over trial (18), with a total of 646 individuals. All the patients in one large study ($n = 185$) had *P. aeruginosa* persistently present in cultures of the airways (15), whereas all the patients in another study ($n = 263$) were not infected with *P. aeruginosa* (17). The other studies included both infected and noninfected patients. Based on our review, the committee believes that there were a sufficient number of individuals with and without *P. aeruginosa* infection studied to develop separate recommendations for these groups. Three of the trials reported significant absolute improvement of FEV_1 between 3.6 and 6.2% (15, 16, 18), and two also reported improvements in FVC (15, 16). The remaining trials reported no statistically significant differences in lung function between azithromycin and placebo (13, 14, 17). However, one of these was a small study designed to measure biomarkers, and lasted only 12 weeks (14). Although the largest trial of individuals without *P. aeruginosa* did not find a change in lung function, there was a 50% decrease in pulmonary exacerbations, which was significant (17). In fact, azithromycin therapy led to decreased exacerbations in four of the five trials reviewed (13, 15–17). A total of 10 studies of azithromycin, with a total of 959 individuals, were analyzed in a recent Cochrane Review (19), which concluded that azithromycin is effective for improving lung function and reducing exacerbations.

There is concern that the chronic use of azithromycin in individuals with occult or active nontuberculous mycobacteria (NTM) infection could lead to resistance, and thus complicate NTM treatment. For this reason, the committee suggests that patients should be screened for NTM before initiating azithromycin, and reassessed periodically at 6- to 12-month intervals. In addition, this monotherapy should be withheld in those infected with NTM.

TABLE 2. SUMMARY OF STUDIES REVIEWED

Treatment Question	Studies	Total (*n*)
Inhaled tobramycin—moderate to severe disease	6 RCT (40–45) 1 RCO (46)	1,110
Inhaled tobramycin—mild disease	3 RCT (47–49)	234
Dornase alfa—moderate to severe disease	8 RCT (50–57) 1 RCO (58)	1,800
Dornase alfa—mild disease	4 RCT (59–62) 3 RCO (63–65)	649
Inhaled hypertonic saline	2 RCT (66, 67) 1 RCO (68)	241
Azithromycin with *P. aeruginosa*	4 RCT (13–15, 17) 1 RCO (18)	271
Azithromycin without *P. aeruginosa*	4 RCT (13, 14, 16, 17) 1 RCO (18)	365
Oral antistaphylococcal antibiotics, prophylactic use	1 RCT (21) 1 RCO (20)	226
Oral antistaphylococcal antibiotics, chronic use	1 RCT (21) 1 RCO (20)	226
Inhaled corticosteroids	6 RCT (69–74) 2 RCO (75, 76)	426
Chronic oral corticosteroids	3 RCT (77–79)	354
Other inhaled antibiotics (Carbenicillin, Ceftazidime, Colistin, Gentamicin)	1 RCT (80) 5 RCO (81–84)	177
Oral antipseudomonal antibiotics	1 RCT (85)	40
Leukotriene modifiers	2 RCO (86, 87)	48
Inhaled or oral *N*-acetylcysteine, or inhaled glutathione	2 RCT (88, 89) 1 RCO (90)	72
Inhaled anticholinergics	0	0
Ivacaftor	3 RCT (25–27) 1 RCO (27)	252
Inhaled aztreonam—moderate to severe disease	3 RCT (30–32)	515
Inhaled aztreonam—mild disease	1 RCT (36)	157
Chronic use of Ibuprofen (age < 18 yr)	4 RCT (7–10)	287
Chronic use of Ibuprofen (age ≥ 18 yr)	1 RCT (7)	41
Chronic inhaled β_2-adrenergic agents	1 RCT (4) 1 RCO (5)	57

Definition of abbreviations: RCO = randomized cross-over trial; RCT = randomized controlled trial.

We developed two recommendations that take *P. aeruginosa* infection into account. The committee rated the certainty of net benefit supporting the use of chronic azithromycin as high for individuals infected with *P. aeruginosa*, and the estimate of benefit was rated as moderate. The certainty of benefit was judged to be moderate for individuals without *P. aeruginosa* infection, and the estimate of net benefit was small.

***Oral antibiotics for* Staphylococcus aureus.** The 2007 guidelines recommended against the prophylactic use of oral antistaphylococcal antibiotics in individuals with CF. We also reviewed the evidence for oral antibiotic treatment of chronic infection with *S. aureus*, which consists of two trials (20, 21). A small cross-over trial ($n = 17$) found that cephalexin therapy for 2 years significantly reduced exacerbations requiring antibiotics in the treatment group compared with the placebo group (25 vs. 53%) and the mean number of hospital admissions (4 vs. 22%) (20). In addition, FEV_1 and FVC also reportedly improved for the cephalexin group (although no further data were provided).

Stutman and coworkers (21) studied chronic prophylaxis with 80–100 mg/kg cephalexin used in 209 young children (<6 yr). A minority of subjects was already infected with *S. aureus* or *P. aeruginosa* or both. The trial showed no benefit in lung function (FEV_1, FVC, $FEF_{25-75\%}$) or exacerbation outcomes. Although there was lower emergence of *S. aureus* in the treated group, these children had a higher rate of *P. aeruginosa* acquisition. A Cochrane Review of antistaphylococcal antibiotics, which evaluated four studies with 303 participants, concluded that the clinical significance of decreased *S. aureus* in treated children is unclear, especially given the potential for increased risk of *P. aeruginosa* infection (22).

Based on the potential for increased *P. aeruginosa* acquisition, the committee again recommended against the prophylactic use of oral antistaphylococcal antibiotics in individuals with CF. The committee determined that the certainty of net benefit is low for individuals chronically infected with *S. aureus*, so there is insufficient evidence to recommend therapy for these individuals.

New Recommendations

Ivacaftor. Ivacaftor is a potentiator that activates defective CF transmembrane conductance regulator (CFTR) at the cell surface (23). The primary target for this therapy is mutated CFTR in which glycine has been replaced by aspartic acid at position 551 (G551D), interfering with the gating of the channel (24).

We identified two RCTs (25, 26) and one randomized cross-over study (25) of ivacaftor. Accurso and coworkers (25) conducted an RCT of 150 and 250 mg of ivacaftor twice daily compared with placebo for 28 days in 19 adults with a least one G551D *CFTR* mutation (25). The 150-mg dose of ivacaftor led to an 8.7% increase in FEV_1 compared with baseline ($P = 0.008$).

Ramsey and coworkers (26) studied the effect of 48 weeks of ivacaftor, 150 mg twice daily, compared with placebo in 161 subjects aged 12 years or older with at least one G551D mutation. The FEV_1 increased 10.4% from baseline in the treated patients compared with −0.2% for those receiving placebo at 24 weeks ($P < 0.001$). Subjects receiving ivacaftor were 55% less likely to have a pulmonary exacerbation than those receiving placebo ($P < 0.001$). There were significant improvements

TABLE 3. SUMMARY OF RECOMMENDATIONS UNCHANGED FROM PREVIOUS GUIDELINES

Treatment	Recommendation	Certainty of Net Benefit	Estimate of Net Benefit	Recommendation
Inhaled tobramycin—moderate to severe disease*	For individuals with CF, 6 years of age and older, with moderate to severe lung disease and *Pseudomonas aeruginosa* persistently present in cultures of the airways, the CF Foundation strongly recommends the chronic use of inhaled tobramycin to improve lung function and quality of life, and reduce exacerbations.	High	Substantial	A
Inhaled tobramycin—mild disease*	For individuals with CF, 6 years of age and older, with mild lung disease and *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation recommends the chronic use of inhaled tobramycin to reduce exacerbations.	Moderate	Moderate	B
Dornase alfa—moderate to severe disease*	For individuals with CF, 6 years of age and older, with moderate to severe lung disease, the CF Foundation strongly recommends the chronic use of dornase alfa to improve lung function, improve the quality of life, and reduce exacerbations.	High	Substantial	A
Dornase alfa—mild disease*	For individuals with CF, 6 years of age and older, with asymptomatic or mild lung disease, the CF Foundation recommends the chronic use of dornase alfa to improve lung function and reduce exacerbations.	High	Moderate	B
Inhaled hypertonic saline	For individuals with CF, 6 years of age and older, the CF Foundation recommends the chronic use of inhaled hypertonic saline to improve lung function and quality of life and reduce exacerbations.	Moderate	Moderate	B
Azithromycin with *P. aeruginosa*	For individuals with CF, 6 years of age and older, with *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation recommends the chronic use of azithromycin to improve lung function and reduce exacerbations.	High	Moderate	B
Oral antistaphylococcal antibiotics, prophylactic use	For individuals with CF, the CF Foundation recommends against the prophylactic use of oral antistaphylococcal antibiotics to improve lung function and quality of life or reduce exacerbations.	Moderate	Negative	D
Inhaled corticosteroids	For individuals with CF, 6 years of age and older, without asthma or allergic bronchopulmonary aspergillosis, the CF Foundation recommends against the routine use of inhaled corticosteroids to improve lung function or quality of life and reduce pulmonary exacerbations.	High	Zero	D
Oral corticosteroids	For individuals with CF, 6 years of age and older, without asthma or allergic bronchopulmonary aspergillosis, the CF Foundation recommends against the chronic use of oral corticosteroids to improve lung function, quality of life or reduce exacerbations.	High	Negative	D
Other inhaled antibiotics	For individuals with CF, 6 years of age and older, with *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of other inhaled antibiotics (i.e., carbenicillin, ceftazidime, colistin, gentamicin) to improve lung function and quality of life or reduce exacerbations.	Low	—	I
Oral antipseudomonal antibiotics	For individuals with CF, 6 years of age and older, with *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation concludes that the evidence is insufficient to recommend for or against the routine use of chronic oral antipseudomonal antibiotics to improve lung function and quality of life or reduce exacerbations.	Low	—	I
Leukotriene modifiers	For individuals with CF, 6 years of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against the routine chronic use of leukotriene modifiers to improve lung function and quality of life or reduce exacerbations.	Low	—	I
Inhaled or oral *N*-acetylcysteine, or inhaled glutathione	For individuals with CF, 6 years of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of inhaled or oral *N*-acetylcysteine or inhaled glutathione to improve lung function and quality of life or reduce exacerbations.	Low	—	I
Inhaled anticholinergics	For individuals with CF, 6 years of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of inhaled anticholinergic bronchodilators to improve lung function and quality of life or reduce exacerbations.	Low	—	I

Definition of abbreviation: CF = cystic fibrosis.

* Severity of lung disease is defined by FEV_1% predicted as follows: normal, >90% predicted; mildly impaired, 70–89% predicted; moderately impaired, 40–69% predicted; and severely impaired, <40% predicted (1).

in QOL, as measured by CF Questionnaire–Revised, as well as nutritional status. The authors observed a 48.1 mmol/L decrease in sweat chloride concentration in treated patients compared with placebo ($P < 0.001$), reflecting the impact of the drug on the basic defect in CF. The incidence of adverse events was similar in the two groups, with a lower proportion of serious adverse events in those treated with ivacaftor compared with placebo (24 vs. 42%).

Data published in abstract form after our systematic review reported similar results in 52 children, aged 6–11 years, with at least one G551D mutation treated with ivacaftor (150 mg twice daily). After 24 weeks of treatment, FEV_1 increased 12.6% from baseline in the group receiving ivacaftor, compared with 0.04% in the placebo group ($P < 0.0001$) (27).

Overall, the committee rated the certainty of net benefit for ivacaftor in patients with at least one G551D *CFTR* mutation as high and the net benefit as substantial. *In vitro* data suggest that there may be a role for ivacaftor in treating other mutations where CFTR protein is present at the cell surface (23), but there is insufficient information to make a recommendation for these

TABLE 4. NEW AND MODIFIED RECOMMENDATIONS

Treatment	Recommendation	Certainty of Net Benefit	Estimate of Net Benefit	Recommendation
Ivacaftor*	For individuals with CF, 6 years of age and older, with at least one G551D *CFTR* mutation, the Pulmonary Clinical Practice Guidelines Committee strongly recommends the chronic use of ivacaftor to improve lung function and quality of life and reduce exacerbations.	High	Substantial	A
Inhaled aztreonam—moderate to severe disease†	For individuals with CF, 6 years of age and older, with moderate to severe lung disease and *Pseudomonas aeruginosa* persistently present in cultures of the airways, the CF Foundation strongly recommends the chronic use of inhaled aztreonam to improve lung function and quality of life.	High	Substantial	A
Inhaled aztreonam—mild disease†	For individuals with CF, 6 years of age and older, with mild lung disease and *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation recommends the chronic use of inhaled aztreonam to improve lung function and quality of life.	Moderate	Moderate	B
Chronic use of ibuprofen (age < 18 yr)	For individuals with CF, between 6 and 17 years of age, with an $FEV_1 \geq 60\%$ predicted, the CF Foundation recommends the chronic use of oral ibuprofen, at a peak plasma concentration of 50–100 μg/ml, to slow the loss of lung function.	Moderate	Moderate	B
Chronic use of ibuprofen (age ≥ 18 yr)	For individuals with CF, 18 years of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of oral ibuprofen to slow the loss of lung function or reduce exacerbations.	Low	—	I
Azithromycin without *P. aeruginosa*	For individuals with CF, 6 years of age and older, without *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation recommends the chronic use of azithromycin should be considered to reduce exacerbations.	Moderate	Small	C
Chronic inhaled β_2-adrenergic receptor agonists	For individuals with CF, 6 years of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against chronic use of inhaled β_2-adrenergic receptor agonists to improve lung function and quality of life or reduce exacerbations.	Low	—	I
Oral antistaphylococcal antibiotics, chronic use	For individuals with CF, 6 years of age and older, with *Staphylococcus aureus* persistently present in cultures of the airways, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of oral antistaphylococcal antibiotics to improve lung function and quality of life or reduce exacerbations.	Low	—	I

For definition of abbreviation, *see* Table 3.

*CF Foundation personnel did not participate in any activity related to ivacaftor.

† Severity of lung disease is defined by FEV_1% predicted as follows: normal, >90% predicted; mildly impaired, 70–89% predicted; moderately impaired, 40–69% predicted; and severely impaired, <40% predicted (1).

mutations at this time. However, there is evidence that the use of ivacaftor alone for individuals with two F508del CFTR mutations, the most frequent genotype in CF, is not effective (28).

Aerosolized aztreonam for moderate to severe disease. *P. aeruginosa* is the most common pathogen in the airways of individuals with CF, and its acquisition is associated with more rapid decline of lung function and decreased survival (29). We identified three studies of inhaled aztreonam using doses ranging from 75 to 225 mg administered two to three times in 515 individuals with FEV_1 between 25 and 75% predicted (30–32). Two trials found statistically significant absolute improvement in FEV_1 after aztreonam treatment for 28 days compared with placebo (6.3–10.3%) (30, 32). A study that assessed lung function after 14 days of treatment found no difference between the groups receiving aztreonam or placebo (31). McCoy and coworkers (30) found that individuals receiving aztreonam twice daily had a statistically prolonged time to an exacerbation compared with placebo (92 vs. 71 d; $P = 0.002$), but no such difference was found for three-times-daily dosing (87 vs. 71 d; $P = 0.182$). Retsch-Bogart and coworkers (32) demonstrated a decrease in hospital days for individuals treated with aztreonam compared with placebo (0.5 vs. 1.5 d; $P = 0.049$). QOL was significantly improved in patients receiving aztreonam compared with placebo (30, 32).

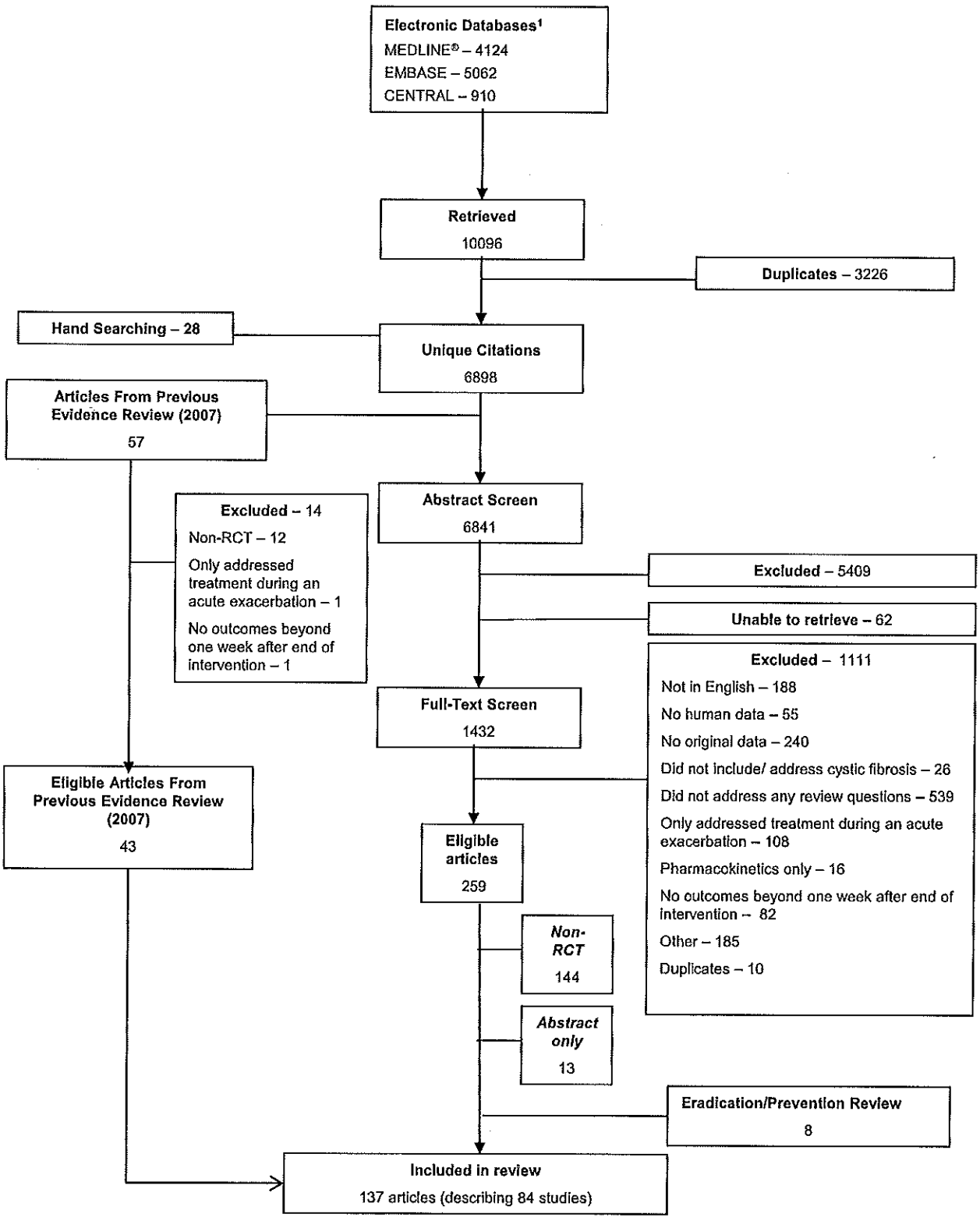
The trials of inhaled aztreonam were well designed and enrolled a large number of subjects. However, they were short term with limited follow up. Long-term, placebo-controlled trials in the current era are not possible, as inhaled antibiotics are standard of care for individuals with *P. aeruginosa* persistently present in airway cultures. An 18-month open label study suggested that long-term use of inhaled aztreonam every other month is safe and effective (33), and not associated with increased resistance to aztreonam (34). In addition, a study of 273 individuals with CF aged 6 years or older demonstrated improved lung function and fewer exacerbations over three 28-day cycles of inhaled aztreonam compared with inhaled tobramycin (35). Therefore, the committee recommends inhaled aztreonam for chronic use with a high degree of certainty for a substantial net benefit.

Aerosolized aztreonam for mild disease. There is one study of inhaled aztreonam in patients with FEV_1 greater than 75% predicted. Wainwright and coworkers (36) studied the effect of 28 days of aztreonam (75 mg thrice daily) on 157 patients, 6 years of age or older, with mild lung disease and *P. aeruginosa* infection. Aztreonam led to a 2.7% relative improvement in FEV_1 compared with placebo ($P = 0.021$) and a modest improvement in QOL. Given this one well designed study with a large number of subjects, the committee rated both the certainty and magnitude of net benefit as moderate.

KEY UNANSWERED QUESTIONS

Many of the issues highlighted in the 2007 version of these guidelines remain unresolved today, including: prioritization of therapies; interactions between medications; effect of bacterial resistance; optimal use of medications in children under 6 years of age; and unintended consequences of long-term medication use. There remain few data to determine the sequence in which medications should be administered for optimal effectiveness. The CF Foundation has recommended the following order of inhaled medications: bronchodilator; hypertonic saline; dornase alfa; airway clearance; and aerosolized antibiotic. We agree that this is a rational approach; however, further study is warranted to assure that it is the optimal approach.

Recommendations for chronic use of medications are based on relatively short trials. The committee recognizes that many



[1]MEDLINE was accessed via PubMed; EMBASE - the Excerpta Medica database, CENTRAL – Cochrane CENTRAL Register of Controlled Trials;

Figure 1. Summary of search and review process.

intervention trials, even those ideally designed, have a finite duration. It is likely that patients will use medications for years or even decades, and that side effects (or benefits) might arise after very long-term use that were not anticipated based on shorter studies. Thus, clinicians must continue to monitor individuals for possible unanticipated side effects of these therapies.

Determining the relative effectiveness of therapies is difficult. There are limited data directly comparing medications, such as mucus-active drugs or antibiotics to one another. In addition, understanding the benefits and potential harms of combination therapy commonly used in practice is critically important. Although traditional RCTs may be impractical in addressing these issues, this could be a fertile area for comparative effectiveness research studies using observational study designs of patient registry data and pragmatic interventional study designs.

In the past, there has been little guidance for the use of medications in children under 6 years of age. More recently, studies have been conducted in young children to determine the effectiveness of medications previously recommended for use in older children and adults (37). We anticipate that, as more medications are studied in young children, evidence-based decision making for this vulnerable population will become easier.

There has been a multiplication of delivery devices for inhaled medications designed to decrease administration time and improve efficacy. Inhaled therapeutics are often paired with a specific device optimized for delivery, creating the potential for less effective delivery when an inappropriate device is used. In addition, using proper administration technique is required to ensure adequate medication delivery. Therefore, it is important for CF health care professionals to educate individuals with CF and their families about proper device use for each prescribed medication.

There are numerous other important questions regarding chronic pulmonary medications for which data from RCTs are lacking. We raise a few of these questions as potential areas of future research.

1. *When should medications be initiated?* As there is likely a component of injury to the airways that rapidly becomes irreversible, it would seem logical that medications with the potential to alter the course of the disease should be initiated at diagnosis or shortly thereafter to prevent injury. However, evaluating medications in young children or those with mild lung disease is challenging due to difficulty in objective measurement of lung disease progression. Studies designed to optimize therapy in these vulnerable populations are key to the ultimate success of future therapies.
2. *How will the use of CFTR-modulating therapies alter the use of other medications?* A new responsibility for CF health care professionals will be to manage expectations of efficacy of CFTR-modulating agents. Even if CFTR function can be returned to near-normal levels, residual damage to airways and other organs will likely necessitate the continuation of many current therapies. It is important to note that individuals participating in studies of ivacaftor continued to use their routine therapies with the exception of hypertonic saline. How to use current therapies in the era of CFTR-modulation therapy will likely become an important new area of research.
3. *How does the burden of therapy affect self-management?* The temptation to add chronic therapies as they become available is great, especially for individuals with more advanced lung disease. However, there are likely to be diminishing returns as the burden of additional therapies decreases an individual's ability to successfully manage any particular therapy. It is clear that decreased adherence to therapies is associated with an increased risk of exacerbations and diminished lung function (38). What is not known is how different combinations of medications will impact self-management, long-term health, and QOL. Studies of strategies to improve self-management and dissemination of those that prove effective will help maximize health.
4. *What is the optimal approach to administration of inhaled antibiotic therapy*? Individuals infected with *P. aeruginosa* typically administer inhaled antibiotics in 28-day, every-other-month cycles. However, it is unknown if this is the best approach for bacterial suppression. For example, as more antibiotics become available, it will be possible to provide continuous therapy by cycling multiple inhaled antibiotics. Studies to determine the optimal approach to initiating and continuing inhaled antibiotics to enhance lung function and minimize bacterial resistance are needed.

CONCLUSIONS

These updated guidelines are based on a systematic review of the published literature. However, any therapeutic decisions must be made individually for each patient. We hope that these recommendations will help CF health care professionals, individuals with CF, and their families make informed health care decisions. We anticipate that these recommendations will be revised as new information becomes available.

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